DOSING REGIMEN ASSOCIATED WITH LONG ACTING INJECTABLE PALIPERIDONE ESTERS

CROSS REFERENCE TO RELATED APPLICATIONS

This application claims the benefit of U.S. Provisional Application 61/014,918, filed on Dec. 19, 2007 and U.S. Provisional Application 61/120,276, filed on Dec. 5, 2008.

FIELD OF THE INVENTION

This invention relates to a method of treating patients in need of treatment with long acting injectable paliperidone palmitate formulations.

BACKGROUND OF THE INVENTION

Antipsychotic medications are the mainstay in the treatment of schizophrenia, schizoaffective disorder, and schizophreniform disorders. Conventional antipsychotics were introduced in the mid-1950s. These typical or first generation drugs are usually effective in controlling the positive symptoms of schizophrenia, but are less effective in moderating the negative symptoms or the cognitive impairment associated with the disease. Atypical antipsychotics or second generation drugs, typified by risperidone and olanzapine, were developed in the 1990s, and are generally characterized by effectiveness against both the positive and negative symptoms associated with schizophrenia.

Paliperidone palmitate is the palmitate ester of paliperidone (9-hydroxy-risperidone), a monoaminergic antagonist that exhibits the characteristic dopamine D_2 and serotonin (5-hydroxytryptamine type 2A) antagonism of the second-generation, atypical antipsychotic drugs. Paliperidone is the major active metabolite of risperidone. Extended release (ER) osmotic controlled release oral delivery (OROS) paliperidone, as a tablet formulation, is marketed in the United States (U.S.) for the treatment of schizophrenia and maintenance of effect.

Paliperidone palmitate is being developed as a long-acting, intramuscular (i.m.), injectable aqueous nanosuspension for the treatment of schizophrenia and other diseases that are normally treated with antipsychotic mediations. Because of extreme low water solubility, paliperidone esters such as paliperidone palmitate dissolve slowly after an i.m. injection before being hydrolyzed to paliperidone and made available in the systemic circulation.

Many patients with these mental illnesses achieve symptom stability with available oral antipsychotic medications; however, it is estimated that up to 75% have difficulty adhering to a daily oral treatment regimen, i.e. compliance problems. Problems with adherence often result in worsening of symptoms, suboptimal treatment response, frequent relapses and re-hospitalizations, and an inability to benefit from rehabilitative and psychosocial therapies.

Paliperidone palmitate injection has been developed to provide sustained plasma concentrations of paliperidone when administered once monthly, which may greatly enhance compliance with dosing. Paliperidone palmitate was formulated as an aqueous nano suspension as is described in U.S. Pat. Nos. 6,577,545 and 6,555,544. However, after the data was analyzed from the clinical trials of this formulation it was discovered that the absorption of paliperidone from these injections was far more complex than was originally anticipated. Additionally, attaining a potential therapeutic plasma level of paliperidone in patients was discovered to be dependent on the site of injection until steady state concentration is reached. Due to the challenging nature of ensuring an optimum plasma concentration-time profile for treating patients with paliperidone it is desirable to develop a dosing regimen that fulfills this goal in patients in need of treatment.

SUMMARY OF THE INVENTION

In one embodiment of the present invention there is provided a dosing regimen for administering paliperidone esters to a psychiatric patient in need of treatment comprising administering intramuscularly in the deltoid a first loading dose from about 100 mg-eq. to about 150 mg-eq. of paliperidone as a paliperidone palmitate formulated in a sustained release formulation on the first day of treatment; administering intramuscularly a second loading dose from about 100 mg to about 150 mg-eq of paliperidone as a paliperidone palmitate formulated in a sustained release formulation between about the 6th to 10th day of treatment; and administering intramuscularly in the gluteal a maintenance dose of about 25 to about 150 mg-eq. of paliperidone as a paliperidone ester in a sustained release formulation on between about the 34^{th} and about the 38th day of treatment.

In one embodiment of the present invention there is provided a dosing regimen for administering paliperidone esters to a psychiatric patient in need of treatment comprising administering intramuscularly in the deltoid a first loading dose from about 100 mg-eq. to about 150 mg-eq. of paliperidone as a paliperidone palmitate formulated in a sustained release formulation on the first day of treatment; administering intramuscularly a second loading dose from about 100 mg to about 150 mg-eq of paliperidone as a paliperidone palmitate formulated in a sustained release formulation between about the 6th to 10th day of treatment; and administering intramuscularly in the gluteal a maintenance dose of about 25 to about 150 mg-eq. of paliperidone as a paliperidone ester in a sustained release formulation approximately monthly from the date of the second loading dose.

In another embodiment of the present invention there is provided a dosing regimen for administering paliperidone palmitate to a psychiatric patient in need of treatment comprising administering intramuscularly in the deltoid of a patient in need of treatment a first loading dose from about 100 mg-eq. to about 150 mg-eq of paliperidone as paliperidone palmitate formulated in a sustained release formulation on the first day of treatment; administering intramuscularly in the deltoid muscle of the patient in need of treatment a second loading dose from about 100 mg-eq. to about 150 mg-eq. of paliperidone as paliperidone palmitate formulated in a sustained release formulation on the eighth day of treatment; and administering intramuscularly in the deltoid or gluteal muscle of the patient in need of treatment a maintenance dose of about 25 mg-eq. to about 75 mg-eq. of paliperidone as paliperidone palmitate in a sustained release formulation on between about the 34th day and the 38th day of treatment.

In another embodiment of the present invention there is provided a dosing regimen for administering paliperidone palmitate to a psychiatric patient in need of treatment comprising administering intramuscularly in the deltoid of a patient in need of treatment a first loading dose of about 150 mg-eq of paliperidone as paliperidone palmitate formulated in a sustained release formulation on the first day of treatment; administering intramuscularly in the deltoid muscle of